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Coronary Artery Changes in Patients with Multisystem Inflammatory Syndrome in Children: Los Angeles Experience

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We compared cardiac findings in patients with multisystem inflammatory syndrome in children and Kawasaki disease in the first 6 months of the 2020 coronavirus disease pandemic to patients with Kawasaki disease during 2016-2019. We saw a high rate of coronary aneurysms in 2020, with a similar rate of coronary involvement but greater volume and incidence of cardiac dysfunction compared with previous years. *(J Pediatr 2021; ■:1-5).*

Multisystem inflammatory syndrome in children (MIS-C) is likely related to a recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] The patients have heterogeneous clinical manifestations, with some Kawasaki disease–like features.[2] It is unclear whether MIS-C and Kawasaki disease are related entities. SARS-CoV-2 infection may be a potent trigger of traditional Kawasaki disease, and others assert that MIS-C has a predilection toward a Kawasaki disease shock syndrome phenotype.[3,4] Cardiac involvement is a frequent finding, often presenting with decreased left ventricular (LV) systolic function and/or sometimes with coronary artery aneurysms (CAAs).[3,5] One study demonstrated a high incidence of cardiogenic shock and low incidence of coronary artery changes.[6] Our experience at Children's Hospital Los Angeles (CHLA) has been different. We sought to compare CAAs and LV changes in patients who have MIS-C/Kawasaki disease phenotypes in the first 6 months of the pandemic in 2020 with patients with Kawasaki disease during the corresponding months of previous years.

Methods

The CHLA Kawasaki disease database contains records of all patients meeting criteria for Kawasaki disease (complete and incomplete) as well as MIS-C. We included all inpatients aged 1 month to 21 years diagnosed with MIS-C (based on meeting Centers for Disease Control and Prevention [CDC] criteria as having positive COVID-19 antibody, a recent positive polymerase chain reaction or antigen test for SARS-CoV-2 on nasopharyngeal specimen, or COVID-19 exposure within the 4 weeks before the onset of symptoms) or Kawasaki disease (defined based on American Heart Association guidelines) between March 1 and August 31, 2020, and then identified those who had coronary artery changes or cardiac dysfunction.[1,5] This group was defined as the postpandemic MIS-C/Kawasaki disease group. Patients with the diagnosis of Kawasaki disease with coronary changes or cardiac dysfunction between March and August of 2016 to 2019 were included for comparison. CAAs were defined as coronary artery z score >2.5 as per Kawasaki disease diagnostic guidelines, and cardiac dysfunction was defined as patients with a reduced LV systolic function (fractional shortening <29% or ejection fraction <55%) measured according to pediatric echocardiogram interpretation guidelines.[5,7] The proximal right coronary artery, left main coronary artery, and left anterior descending coronary artery were remeasured in each patient by a single reviewer, for consistency. Then, z scores were obtained using values from Boston Children's Hospital z score system.[8] SAS JMP software, version 14 (SAS Institute) was used for statistical analysis. A comparison was made between those in the pre- and postpandemic groups using Fisher exact and χ^2 tests for categorical variables and a 2-tailed Student *t* test for parametric variables. A *P* value of <.05 was considered significant. This study was approved by the institutional review board at CHLA (CHLA-20-00210) and was exempt from parental consent, given that all study measures were obtained in the course of clinical care and cases were deidentified when entered into the dataset.

CAA	Coronary artery aneurysm
CDC	Centers for Disease Control and Prevention
CHLA	Children's Hospital Los Angeles
COVID-19	Coronavirus disease 2019
IgG	Immunoglobulin G
LV	Left ventricular
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Results

There were 57 patients with postpandemic MIS-C/Kawasaki disease in March through August 2020, of whom 28 (49%) had cardiac involvement. Of these, 22 (39%) had CAA and

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11 (19%) had LV dysfunction (5 overlap with both CAA and LV dysfunction). Of the 57 cases in the postpandemic MIS-C/Kawasaki disease group, 27 had positive SARS-CoV-2 immunoglobulin G (IgG) antibody detected and 1 had confirmed COVID-19 parental exposure but a negative antibody test; these 28 met CDC criteria for MIS-C. There were 26 additional cases with negative SARS-CoV-2 IgG antibodies, and 3 had no antibody testing. Of the 27 patients with positive SARS-CoV-2 IgG, 19 (70%) had no recognized history of illness or known ill contacts, and 8 had some history (1 with known previous COVID-19, 1 with previous illness not tested for COVID-19, 2 with known COVID-19 exposure, 4 with known sick contacts not tested for COVID-19). Of the 28 patients with cardiac involvement in the postpandemic group, 19 met CDC criteria for MIS-C, 1 had no antibody test, and 8 had negative antibodies. Of the entire postpandemic MIS-C/Kawasaki disease group, 42 met Kawasaki disease criteria, including 17 meeting complete Kawasaki disease criteria and 25 meeting incomplete Kawasaki disease criteria. Of those meeting criteria for incomplete Kawasaki disease, 16 did so based on symptoms and laboratory results alone, and 9 required a coronary finding to meet incomplete Kawasaki disease criteria.[5] Of the 42 who met Kawasaki disease criteria, 14 additionally met MIS-C criteria with positive SARS-CoV-2 antibodies (5 with complete Kawasaki disease, 9 with incomplete Kawasaki disease), 3 were not tested for SARS-CoV-2 antibodies, and 25 had negative SARS-CoV-2 antibodies. An additional 14 subjects met only MIS-C criteria (13 with antibodies and 1 with parental exposure) and 1 was treated for MIS-C due to clinical and laboratory findings but negative antibodies after a previous nonconfirmed COVID-19–like illness.

There were 98 patients with prepandemic Kawasaki disease between March and August 2016 and 2019, of whom 33 (34%) had cardiac involvement. Of these 98 cases, 30 (31%) had CAA and 3 (3%) had CAA plus LV dysfunction; none had isolated LV dysfunction. The number of patients with MIS-C/Kawasaki disease in March through August 2020 with cardiac involvement was approximately 3-4 times the number of patients with Kawasaki disease and cardiac abnormalities in each previous year March through August of 2016-2019 (**Figure**). The proportion of patients with coronary aneurysms was similar between the groups, 34% (33/98) prepandemic and 39% (22/57) postpandemic, $P = .6$, and the postpandemic group had a significantly greater rate of LV dysfunction (19% postpandemic vs 3% prepandemic, $P \leq .0001$). Between the 2 groups, there was no significant difference in the number of small, medium, or giant coronary aneurysms (**Table**, $P = .35$). Postpandemic CAAs were seen in patients meeting MIS-C criteria as well as those meeting Kawasaki disease criteria, including 3 of 4 patients with giant CAA, 2 of 5 with medium CAA, and 7 of 13 with small CAA having positive SARS-CoV-2 antibodies or parental COVID-19 exposure. The largest postpandemic z scores for each coronary artery included right coronary artery z score +34, left main coronary artery +10.5, and left anterior descending +28.6

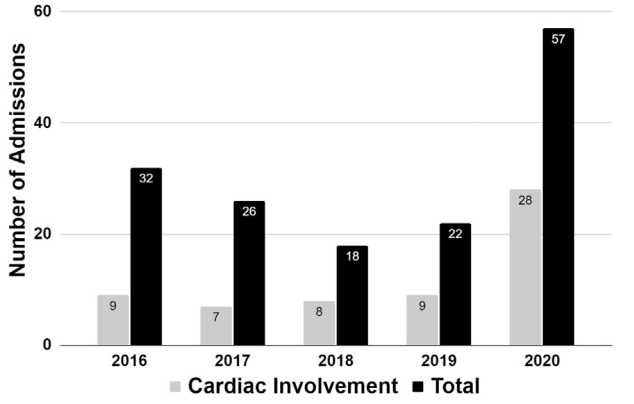

Figure. The number of admissions for Kawasaki disease/MIS-C during the months of March through August during 2020 and for Kawasaki disease during the same months over the last 5 years at CHLA.

compared with z scores in the prepandemic group's CAAs of +18.8, +9.11, and +10.9, respectively. The median age of patients with isolated coronary changes between both groups was not significant, 2.3 years prepandemic compared with 1.3 years in the postpandemic group ($P = .83$). There was a significant difference in the age of patients with LV dysfunction, as postpandemic patients with MIS-C/Kawasaki disease with LV dysfunction were significantly older (median 10 years of age) than those in the prepandemic group (4 years of age); $P = .03$. There was no difference between the 2 groups in the median size of CAA of the left main ($P = .62$), left anterior descending ($P = .12$), or right coronary artery ($P = .96$) segments (**Table**).

The subgroup of patients within the postpandemic group who met CDC criteria for MIS-C and additionally had cardiac involvement (N = 19) was additionally compared with the prepandemic group (**Table**). In this subgroup, 13 patients had CAA (46% of the 28 patients meeting CDC criteria for MIS-C), and all 11 of the postpandemic LV dysfunction subjects met MIS-C criteria (39% of 28), with 5 overlapping both CAA and LV dysfunction groups. The proportion of patients with CAA was not statistically different between the groups (**Table**, 34% prepandemic vs 43% MIS-C, $P = .38$), and the postpandemic MIS-C subgroup continued to have a significantly greater rate of LV dysfunction (3% prepandemic, vs 39% MIS-C, $P < .0001$). Between the 2 groups, there was no significant difference in the number of small, medium, or giant CAA (**Table**, $P = .19$). There continued to be no significant difference in median age among those with isolated CAA (2.4 years prepandemic vs 0.9 years postpandemic MIS-C, $P = .67$), and there was again seen to be a significantly older age in MIS-C patients with LV dysfunction (2.4 years prepandemic vs 8 years MIS-C, $P = .005$), as well as greater weight and height in the MIS-C subgroup with cardiac involvement, likely driven by the higher age (**Table**). In

Table. The demographic and echocardiographic comparison between patients with prepandemic Kawasaki disease and postpandemic MIS-C/Kawasaki disease with cardiac involvement

Characteristics	Prepandemic Kawasaki disease with cardiac involvement, n = 33	Postpandemic MIS-C/Kawasaki disease with cardiac involvement, n = 28	*P* values (pre- vs post-)	Postpandemic subset meeting CDC definition of MIS-C, with cardiac involvement, n = 19	*P* values (pre- vs subset)
Male (%)	18 (55%)	18 (64%)	.6	12 (66%)	.57
Median weight, g	13 (IQR 10.5-17.7)	21.6 (IQR 10.4-46.9)	**.04**	35.1 (IQR 11-55)	**.003**
Median height, cm	88 (IQR 77.5-107)	87.5 (IQR 77-106)	.06	121 (IQR 82-160)	**.006**
Median age, y	2.4 (IQR 0.9-4)	5 (IQR 0.9-11)	**.04**	8 (IQR 0.9-13)	**.005**
Age of patients with LV dysfunction, y	4 (IQR 4-7)	10 (IQR 8-15)	**.03**	10 (IQR 8-15)	**.03**
Age of patients with isolated CAA, y	2.3 (IQR 0.7-3) N = 30	1.3 (IQR 0.7-5) N = 17	.83	0.9 (IQR 0.7-7.29) N = 8	.67
Number of patients with LV dysfunction	3 (3% of 98)	11 (19% of 57)	**.0067**	11 (39% of 28)	**<.0001**
Number of patients with pericardial effusion	8 (8% of 98)	4 (7% of 57)	1	4 (14% of 28)	.46
Number of patients with CAA	33 (34% of 98)	22 (39% of 57)	.6	12 (43% of 28)	.38
Small CAA	23 (70% of 33)	13 (59% of 22)	.35*	7 (58% of 12)	.19*
Medium CAA	8 (24% of 33)	5 (23% of 22)		2 (17% of 12)	
Giant CAA	2 (6% of 33)	4 (18% of 22)		3 (25% of 12)	
Proximal right coronary artery z score	+2.6 (IQR 1.1-3.9) range: −0.7 to18.8	+2.5 (IQR 0.4-7.5) range: −1.6 to 34.1	.96	+2.5 (IQR 1.3-5.3) range: −1.6 to 34.1	.62
Left main coronary artery z score	+1.5 (IQR 0.5-3.1) range: −1.0 to 9.1	+1.9 (IQR 1.2-2.42) range: −0.2 to 10.6	.62	+2.0 (IQR 1.4-2.5) range: −0.2 to 9.8	.46
Left anterior descending coronary artery z score	+3.0 (IQR 1.6-4.3) range: −2 to 10.9	+4.0 (IQR 2.5- 5.6) range: 0.78-28.6	.12	+4.6 (IQR 2.6-8.1) range: 1.4-28.6	**.03**

P values which reach statistical significance are bolded. *P* values <.05 were considered significant.
**P* value based on χ^2 analysis among the 3 sizes of coronary aneurysms.

isolation, the Z scores for proximal right ($P = .62$) and left main ($P = .46$) coronary artery sizes were not significantly different, but there was a significantly larger median left anterior descending coronary Z score in the post-pandemic MIS-C subgroup (Left anterior descending coronary artery z score +3.0 vs +4.6, $P = .03$).

Discussion

Our data demonstrate that during the first 6 months of the COVID-19 pandemic, although the number of cases of MIS-C/Kawasaki disease were greater than those of Kawasaki disease in previous years, the proportion of those with coronary artery findings and the types of aneurysms did not significantly differ from those who presented with Kawasaki disease during the same months before the pandemic. We found a greater incidence of LV dysfunction in our postpandemic MIS-C/Kawasaki disease group compared with prepandemic, and all LV dysfunction was seen in patients meeting CDC criteria for MIS-C. The subgroup patients meeting CDC criteria for MIS-C in the first 6 months of the pandemic who had cardiac findings included infants, and we saw major coronary artery changes, including giant CAA with dramatically high z scores exceeding +30 in some subjects with MIS-C.

Our findings have notable differences from previous reports and further raise the question of whether MIS-C is a new or related pathologic mechanism to Kawasaki disease.[9,10] Matsubara et al describe MIS-C as having a predominance of LV dysfunction independent of coronary artery changes and report a single CAA among 28 MIS-C cases.[6] One of the first descriptions of MIS-C from the Italian epicenter of COVID-19 mentioned 2 subjects with CAA >4 mm of 10 total cases.[9] Another study from France in the early pandemic described 21 cases of MIS-C, of whom 5 had coronary dilation but no aneurysms.[11] A study from London described 8 of 58 patients with MIS-C and CAA, and the CDC reported that 16.5% of 1733 patients with MIS-C had coronary involvement.[12,13] These 5 studies have rates of coronary changes of 4%, 20%, 24%, 14%, and 16.5% respectively,[6,9,11-13] in contrast to our study, which had a greater rate of CAA at 39% in the full MIS-C/Kawasaki disease group and 43% in the subgroup meeting CDC criteria for MIS-C.

The reasons for the differences seen in our population are unclear. One possible explanation is the variability in regional environmental triggers as described for Kawasaki disease.[14] The differences may be indicative of ethnic population differences as well, as Los Angeles has a large Hispanic population that is known to be particularly affected by MIS-C.[2,13] Our center is also a large referral center for Kawasaki disease and MIS-C and located in a large metropolitan area as well as covering a large geographic area within Southern California, and we have a high rate of CAA in our Kawasaki disease population at baseline as well. We additionally saw several patients with coexisting LV dysfunction and CAA in our MIS-C group, which was only seen in 2 patients in the Italian study and no patients in the other studies.[6,9,11] These differences distinguish our experience from other parts of the world.

A limitation in our study is that we combined patients with Kawasaki disease and MIS-C into a single postpandemic group. However, in a subgroup analysis of those meeting CDC criteria for MIS-C, the results compared with the prepandemic did not significantly differ from the MIS-C/Kawasaki disease combined results compared with prepandemic. Many of our subjects fit under diagnostic criteria for both diagnoses. In April 2020, we had a high seroprevalence of SARS-CoV-2 in Los Angeles County, such that there is potential to incompletely capture past exposure to satisfy the CDC criteria for MIS-C.[1,15] We had many subjects with positive SARS-CoV-2 antibodies who were unaware of having COVID-19 previously. If Kawasaki disease and MIS-C have greater differences than similarities, then this study may underestimate those differences. We believe this is less likely because the majority of the patients in the postpandemic group with cardiac involvement were found to be positive for SARS-CoV-2 antibodies. In addition, we were not able to report race and ethnicity information in our cohorts, as it was incompletely captured in our electronic medical record.

In conclusion, it is important to be aware of the heterogeneity of the presentation of MIS-C cardiac findings. We recommend that patients with MIS-C undergo thorough echocardiographic examinations that include detailed evaluation of coronary artery dimensions, even in patients who have LV dysfunction. ■

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References

1. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Accessed May 26, 2020. https://www.cdc.gov/mis/mis-c/hcp/index.html
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.
3. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020;382:1370.
4. Yeo WS, Ng QX. Distinguishing between typical Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2. Med Hypotheses 2020;144:110263.
5. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.
6. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76:1947-61.
7. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the

performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010;23:465-95; quiz 576-7.
8. Colan SD. Normal echocardiographic values for cardiovascular structures. In: Lai WW, Cohen MS, Geva T, Mertens L, eds. Echocardiography in pediatric and congenital heart disease. West Sussex, UK: Wiley-Blackwell; 2009. p. 765.
9. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771-8.
10. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183:968-81.e7.
11. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094.
12. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259-69.
13. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr 2021;175:837-45.
14. Rypdal M, Rypdal V, Burney JA, Cayan D, Bainto E, Skochko S, et al. Clustering and climate associations of Kawasaki Disease in San Diego County suggest environmental triggers. Sci Rep 2018;8:16140-9.
15. Sood N, Simon P, Ebner P, Eichner D, Reynolds J, Bendavid E, et al. Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, on April 10-11, 2020. JAMA 2020;323:2425-7.